

SEARLE

March 29, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 982-4701

Subject: Docket No. 98D-0994

Gentlemen:

Searle's recognizes that the BACPAC I draft guidance is a significant improvement to existing regulatory guidance. Searle also provides the following comments relative to the BACPAC I draft guidance.

GENERAL COMMENTS

In general, Searle objects to BACPAC I guidance requirements to provide registration commitments for data and information not required for submission in an original NDA. Requests for descriptions of analytical test methods and method validation for intermediates, detailed equipment descriptions, certificates of analysis for raw materials and lists of vendors for starting materials are more appropriate as demonstration of compliance to GMP than as commitments to the registration. Although this information may serve as substantiation for changes and modifications to the drug substance manufacturing process and is typically available for an inspection, the nature and scope of BACPAC I does not warrant requests for commitments beyond those established in an original NDA to which such changes are adequately satisfied by demonstration of chemical equivalence. In addition, registration documentation necessary to adhere to these requests does not reflect a reduction in paperwork in accordance with the spirit of FDAMA, but rather an escalation of paperwork.

SPECIFIC COMMENTS

Lines 120-121

Replace the sentence: "*When new methods are developed for this purpose, validation data should be provided*" with "New methods that are developed should be appropriately validated for the intended purpose and the validation data should be available for inspection."

Lines 243 - 245 (applicable to Lines 289, 333, 348, 375, 417, 456, 511)

Validation of in-process test methods or release tests for intermediates is not routinely included in NDA submissions. We recommend deleting the sentence; "*Validation data should be provided . . .*" and replacing it with; "**These methods should be appropriately validated.**"

Lines 259 - 260 (applicable to Lines 259, 305, 391, 439, 477, 534)

The compilation of batch data should be sufficient for evaluating site changes as well.

98D-0994

C15

Line 267

The recommendations for CBE supplement should be clarified. A supplement “with changes being effected” (CBE) should be required only if equivalence is not demonstrated. If equivalence is demonstrated then information describing a manufacturing site change (through preparation of the Final Intermediate) will be provided in the Annual Report.

Physical properties of the final intermediate are not important. Also, if equivalence is demonstrated do we have to say anything about impurity levels.

Line 328 - 329

The following statement seems to contradict subsequent information under Lines 338 and 354:

“Specification changes for the Final Intermediate are not included in this guidance.”

Frequently changes to test methods require adjustments or changes to specifications and acceptance criteria limits for the Final as well as other intermediates. We do not believe we can entirely divorce method changes from specifications changes. We request additional clarity regarding this statement, or alternatively, deletion of this provision.

Lines 349 - 350 (applicable to Line 391)

A compilation of batch data is sufficient to demonstrate changes. The sponsor should be permitted to provide certificates of analysis or compilation of batch data as substantiation for changes to intermediates.

Line 354 (applicable to Line 395)

Singular modifications or changes to intermediate specifications should qualify for notification to the Annual Report and not via submission as a supplement with changes being effected (CBE).

Line 442

For all changes to the manufacturing process where chemical and impurity profile equivalence is demonstrated prior to the final API, notification of the change in the Annual Report is appropriate. For changes to the manufacturing process that require equivalence evaluation on the final API, a supplement with changes being effected (CBE) is recommended.

Line 480

For changes to the synthetic route where equivalence is demonstrated prior the final API, notification of the change to the Annual Report is appropriate. For changes to the synthetic route that require equivalence evaluation on the final API, a supplement with changes being effected (CBE) is recommended.

Dockets Management Branch (HFA-305)

March 29, 1999

Page 3

Lines 501 - 502

Delete the entire bullet:

“A list of sources (including commercial vendors and contract manufacturers of the redefined starting material.”

The sponsor and/or manufacturer should provide adequate assurance that the starting materials are appropriately controlled. Alternatively we recommend that the sponsors adhere to the following commitment:

“The suppliers of the starting materials used in the synthetic manufacture of the drug substance will be incorporated into the sponsor’s material audit program and monitored in accordance with vendor audit criteria to ensure adequate and consistent identity, purity and quality.”

The vendor audit criteria or program should be available for PAI but not supplied as registration commitments.

Lines 503 - 504

Delete the entire bullet. Assurance that adequate change control for a new or alternative vendor or supplier is an operational function performed in accordance with the establishment of an appropriate vendor audit program and adherence to GMP and should not be included among registration commitments.

Line 581 - 582

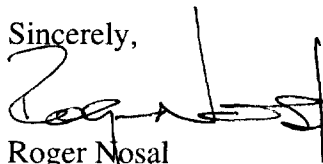
Amend the definition of Final Intermediate to include:

“The final step forming the new drug substance must involve covalent bond formation 'or breaking'; ionic bond formation (i.e., making the salt of a compound) does not qualify.”

Hydrolysis of an ester followed by isolation of a carboxylic acid salt is an example.

If you have any questions regarding Searle’s comments on the BACPAC I draft guidance, please contact me at (847) 982-7250.

Sincerely,



Roger Nosal
Director, Chemistry, Manufacturing
and Controls
Worldwide Regulatory Affairs

RN/anb

[®]
al Express

M. PATEL
SEARLE
4901 SEARLE PARKWAY
SKOKIE
(847)982-8693

IL 60077

SHIP DATE: 29MAR99
ACC# 169850380

ACTUAL WGT: 1 LBS SCALE

SEE ADDRESS LABEL ON PACKAGE
FOR THIS SHIPMENT TO
MD 20852

4202 1840 0571

FedEx.

4202 1840 0571

REF: 6553 N. POPOVICH

PRIORITY OVERNIGHT TUE.

CAD# 0080746 29MAR99

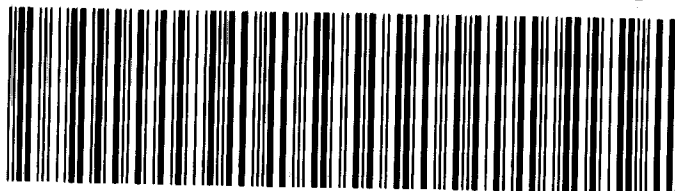
TRK# 4202 1840 0571 Form 0201

Deliver by:
30MAR99

IAD

20852 -MD-US

XA EDGA



FDA
THIS PACKAGE
HAS BEEN
X-RAYED

SEARLE

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

a MONSANTO  company

World On Time[®]